Review

Blood pressure alterations in patients with type 1 diabetes

Alteraciones de la presión arterial en pacientes con diabetes tipo 1

F.J. Vilchez López,1 C. Coserria Sánchez,2 F. Carral Sanlaureano,3 M. Aguilar Diosdado4

Abstract

Hypertension and subclinical alterations of blood pressure (non-dipper pattern) increase the risk of chronic diabetes complications. In spite of this risk, there are few studies that analyze this problem in type 1 diabetic patients. Because of this, we have made an exhaustive search about this item in bibliographic databases (PubMed, Ovid). Prevalence of hypertension and non-dipper pattern is different depending on the methodology and population characteristics (hypertension: 8-58%; non-dipper pattern: 18-78%). Non-dipper pattern increases significantly the risk of microalbuminuria and retinopathy. Although there is evidence about the beneficial effect of a strict control of hypertension, at the moment we do not know exactly the beneficial effect of treating subclinical alterations of blood pressure in patient with values at normal range during standard measurement.

Keywords: ambulatory blood pressure monitoring, diabetes mellitus, non-dipper.

Resumen

La hipertensión arterial (HTA) incrementa de forma significativa el riesgo de complicaciones crónicas de la diabetes. Mediante la monitorización ambulatoria de presión arterial (MAPA) es posible detectar alteraciones subclínicas de la presión arterial (PA), como el patrón no dipper, que pasan desapercibidas con la toma aislada, y que son más prevalentes en pacientes con diabetes que en la población general. A pesar de su relevancia, son escasos los datos disponibles a este respecto en pacientes con diabetes tipo 1 (DM1). Por este motivo, se ha realizado un exhaustivo análisis de la bibliografía (PubMed, Ovid). La prevalencia de HTA y de patrón no dipper difieren según la metodología del estudio y las características de la población analizada (HTA: 8-58%; patrón no dipper: 18-78%). La presencia de patrón no dipper incrementa significativamente el riesgo de microalbuminuria y retinopatía. Aunque el control estricto de la HTA disminuye la aparición de complicaciones crónicas de la diabetes, no hay evidencias de que el tratamiento de las alteraciones subclínicas de la PA, detectadas mediante MAPA en pacientes normotensos, disminuya la tasa de complicaciones, por lo que es necesario llevar a cabo estudios prospectivos para aclarar esta cuestión.

Palabras clave: monitorización ambulatoria de la presión arterial, diabetes mellitus, patrón no dipper.

Introduction

The blood hypertension (BHT) increases potentially the risk of onset and progression of chronic complications in diabetic patients.1,2 It is considered that the increase of 20 mmHg as from 115 mmHg in the systolic blood pressure or 10 from 75 mmHg in the diastolic, duplicates the risk of cardiovascular events,3 and that between 35 and 75% of the diabetes complications are due to the coexistence of BHT.1 Moreover, the strict control of the blood pressure (BP) decreases significantly the morbidity and the mortality, both in patients with diabetes and in the general population.3,4
The prevalence of the BHT in patients with T1D differs significantly in the different publications according to the characteristics of the studied populations and the measurement method that is being used. Moreover, the normality criteria used vary depending on the date of each study, though the most common ones are 140/90 and 130/85 mmHg. At present, most of the scientific societies accept that the control objective of the BP in diabetic patients shall be lower than 130/80 mmHg.5,6

The use of the ambulatory blood pressure monitoring (ABPM) is a more and more common technique that allows to detect subclinical alterations of the pressure values, as the no dipper phenomenon or the masked BHT, that pass unnoticed in the isolated measurement of the BP. The results of the observational studies published during the last years suggest that the presence of these alterations is not innocuous, but it has an important repercussion. Thus, the loss of circadian rhythm of the BP increases the risk of developing complications, mainly microangiopathic, in diabetic patients.7,8

The presence of these alterations in the usual follow-up is not usually evaluated among the patients with T1D. We count with scarce information about the prevalence and the potential relevance as regards to the development of diabetes chronic complications.

The objective of this revision is to analyze the BHT prevalence and the subclinical pressure alterations in patients with T1D, as well as their clinical implications as regards to the development of diabetes chronic complications.

Material and methods

• Inclusion criteria. Randomized, prospective clinical studies, not prospective or not randomized clinical studies, systematic revisions, consensus documents of scientific societies and expert opinions. The search was limited to studies published in English and Spanish.

• Exclusion criteria. Not clinical studies, individual opinions.

Methods

Bibliographical search and revision of the works that comply with the inclusion criteria published up to December 2008 in PubMed and Ovid.

• Search terms: T1D; hypertension, blood pressure, circadian rhythm of blood pressure, non-dipper, ABPM, nephropathy, retinopathy, neuropathy, cardiovascular disease.

The clinical studies with greater interest have been chosen regarding both to the analysis of the BHT prevalence, and the pressure alterations detected by means of ABPM in patients with T1D; moreover those studies that related these alterations with triggering potential factors and with diabetes chronic complications have also been chosen.

The search was completed with the manual revision of the relevant quotations that appeared in the bibliography of the chosen articles.

Results

Blood pressure measurement methods

At present, we count with different techniques to measure the BP in ambulatory patients: the isolated BP measurement, the self-measurement blood pressure at home (SMBP) and the ABPM9 (table 1).

The most frequent technique is the isolated BP measurement, though this determination is usually left out in many patients with T1D during the medical visit,10 probably because these patients are considered normotensive, considering that they are usually young and without symptoms of cardiovascular disease. On the other hand, this technique does not reflect the variability of the BP: intrinsic factors to the patient himself, mistakes in the measurement technique and the turn of the observer induce the BHT diagnosis in 20-25% of the normotensive patients (isolated BHT at the office or white coat BHT).11

The SMBP and the ABPM present several advantages compared to the isolated BP measurement: more reproducibility, limitation of the observer bias and lower alert reaction of the patient. Moreover, the results are better correlated to the affection of target organs and the
cardiovascular mortality, and provide valuable information about the effect of the hypertensive drugs. Moreover, the ABPM is the only technique that informs the BP while the patient carries out his daily activity and during the sleeping period, showing also the integrity or not of the circadian rhythm of the BP.9,12-16

The SMBP and the ABPM show also some limitations. The normality criteria, lower than those stated for the isolated measurement, are clearly determined for the general population, but we do not count with specific limits for the diabetic patients.3,16 In order to define the presence of BHT it has to be considered the BP mean during the activity period, as the 24-hour mean values might be affected by the higher or lower duration of the night rest and the sleep.15 Table 2 depicts the BP normality limits for the general population in each of the mentioned techniques.16 Other inconveniences of the ABPM are the possibility of interfering in the work or the sleep, the intolerance cases, its high cost and its limited reproducibility, though this is higher than the one obtained with the BP isolated measurements.17,19

**BHT prevalence in patients with T1D**

There are only a few studies, which have dealt with the prevalence and the level of BHT in patients with T1D. Below, the main results are detailed.

In the Pittsburg Epidemiology of Diabetes Complications Study, published in 2001, 386 patients with T1D have been included (of 28 years of age and 20 years of mean evolution), observing an initial BHT prevalence of 12.9% (criterion: BP >140/90 mmHg or under the hypo-pressure treatment) that increased to 29% after 10 years of follow-up. Only 50% of the patients show BHT under control.20

Later, the Coronary Artery Calcification in type 1 diabetes Study (CACT1) analyzed a series of 652 patients with T1D aged 37 and with 23 years of diabetes mean evolution.21 43% of the patients was hypertensive (criterion: BP >130/85 mmHg) and though 83% received pharmacology treatment, only 55% complied with the control criteria according to the JNC-6 (recommended BP <130/85 mmHg).22

In Europe, the EURODIAB IDDM Complications Study23,24 analyzed the evolution of the BHT prevalence in a cohort of patients with T1D in the periods between 1989-1990 and 1997-1999. In the initial evaluation, 3,250 patients with T1D were studied, with a mean age of 33 years and 15 years of evolution, being 22% catalogued as hypertensive (criterion: BP >140/90 mmHg or under hypotensive treatment). Stratifying it according to the level of albuminuria, the BHT prevalence increased 15.2% in patients with normal albuminuria and 28.9 and 64.7% in patients with micro and macro-albuminuria, respectively.23 In the 1,886 patients evaluated 10 years after (1997-1999), the BHT prevalence increased up to 34%, though the increase was similar in all the age groups and the percentage of patients with diabetic nephropathy was not modified significantly. Likewise, the percentage of patients treated pharmacologically increased from 40 to 60%, and the rate of patients with BP levels lower than 130/85 mmHg passed from 12 to 28%.24
In our country, at the end of the 90s, an observational and multicenter study has been performed in which 18 hospitals of several autonomous communities took place (DIAMANTE study), that objective was to evaluate the prevalence of the diabetic nephropathy among the patients with T1D. Together, 1,821 patients have been analyzed with a mean age of 30.5 and 14 years of evolution, from which 22% showed diabetic nephropathy (14.1% microalbuminuria, 5% macroalbuminuria and 3.5% renal failure). The 11% of the patients were hypertensive (criterion: BP >140/90 mmHg). When stratifying them by the nephropathy level, the BHT criterion was complied by 4% of the patients with normal albuminuria, 14.8% of the patients with micro-albuminuria and 70% of the patients with evident nephropathy (albuminuria or renal failure). The 14% was under hypotensive treatment, mainly with ACEI.

A similar study performed in the Canary Islands, which included 142 patients with a mean age of 28 years and 11 years of evolution, detected a global BHT prevalence of 59% (criterion: BP >130/85 mmHg). When stratifying them by albuminuria level the BHT criterion was complied by 4% of the patients with normal albuminuria, 71.4% of the patients with micro-albuminuria and 83.3% of the patients with evident nephropathy.

Finally, the recently published study EDIC (Epidemiology of Diabetes Interventions and Complications Study) provides interesting data about the follow-up of 1,375 patients who have been previously included in the DCCT (Diabetes Control and Complications Trial). After a mean of 15.8 years of follow-up, 45.8% have been diagnosed as hypertensive (criterion: BP >140/90 in at least 2 occasions or hypotensive taking). The 21.1% of the patients developed micro-albuminuria and 6.5% macro-albuminuria. In spite that, since the end of the DCCT, all the patients included in the EDIC followed an intensive insulin therapy, the BHT incidence was of 24% lower between the group of patients assigned to the intensive group during the DCCT compared to the group that received conventional treatment.

Table 3 sums comparatively up the results of the main works published up to present about the BHT in patients with T1D.

### Table 3. BHT prevalence studies in patients with T1D

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Age (years)</th>
<th>Years of evolution</th>
<th>BHT (%)</th>
<th>Albuminuria (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study DIAMANTE⁵ (1997)</td>
<td>1,822</td>
<td>30.5 ± 9.7</td>
<td>14.1 ± 9.2</td>
<td>11.3</td>
<td>22.6</td>
</tr>
<tr>
<td>De Pablos et al.⁶ (1997)</td>
<td>142</td>
<td>27.9 ± 11.5</td>
<td>10.9 ± 7.6</td>
<td>58.7</td>
<td>36.7</td>
</tr>
<tr>
<td>Collado-Mesa et al.⁷ (1999)</td>
<td>3,250</td>
<td>33 ± 1</td>
<td>15 ± 10</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Zgibor et al.⁸ (2001)</td>
<td>386</td>
<td>28</td>
<td>30</td>
<td>12.9</td>
<td>–</td>
</tr>
<tr>
<td>Soedamah-Muthu et al.⁹ (2002)</td>
<td>1,866</td>
<td>40 ± 10</td>
<td>22 ± 9</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Maahs et al.⁵  (2005)</td>
<td>652</td>
<td>37 ± 9</td>
<td>23.2 ± 8.9</td>
<td>43</td>
<td>21.8</td>
</tr>
<tr>
<td>Baena et al.⁷  (2008)</td>
<td>489</td>
<td>33.6</td>
<td>16.6</td>
<td>8.27</td>
<td>8.6</td>
</tr>
<tr>
<td>De Boer et al.⁷  (2008)</td>
<td>1,375</td>
<td>42.8</td>
<td>19.8</td>
<td>44</td>
<td>27.6</td>
</tr>
</tbody>
</table>

*These percentages refer to the total of individuals with albuminuria in different stages.

### Alterations in the circadian rhythm of blood pressure in patients with T1D

The BP is not consistent throughout the day, but it presents a circadian rhythm: it reaches a minimum during the first hours of sleep and increases during the first hours in the morning, coinciding with the transition between the sleep and the wakefulness. The mean BP difference, during the day and night, is from 10 to 20%, both in healthy subjects⁹ and in hypertensive subjects,²⁸ physiological situation known as dipper pattern. Night decreases lower than 10% define a non-dipper pattern (figure 1).

### Etiopathogenic factors

It has been described that the non-dipper pattern appears with a higher frequency in blacks, in patients treated with steroids, in renal failure and even, in healthy individuals if the daytime activity has been intense or if they suffer sleep alterations.²⁸,²⁹
However, the etiopathogenic factors implied in the onset of the non-dipper phenomenon in patients with T1D are not really known. The autonomous neuropathy is stated as one of the most relevant. In a recent series of 117 patients with T1D, the non-dipper was more prevalent in those who had autonomous neuropathy. In a similar way, another study of 47 diabetic patients, normotensive, and with normal albuminuria, showed a lower night reduction of SBP and DBP among those with autonomous neuropathy (night decrease of SBP and DBP in patients with neuropathy versus patients without neuropathy, respectively: 3.4 ± 9.3 versus 9.7 ± 5.6 mmHg and 8.3 ± 9.2 versus 16.0 ± 6.0 mmHg).

At present, it has not been proved conclusively that diabetes metabolic control, age, disease evolution time, type of insulin therapy and smoking habit are directly related to the onset of pressure alterations detected in the ABPM.

Prevalence

Though the prevalence of the non-dipper pattern is more frequent among patients with diabetes and nephropathy, the studies that have evaluated this question in patients with normal pressure and normal albuminuria with T1D are scarce. The main ones are presented below.

In 1994, Gilbert et al. compared the results of the ABPM of 13 normotensive and normal albuminuria patients with T1D with a control group of 14 subjects without diabetes. The non-dipper phenomenon was defined as the presence of a BP night reduction lower than 10% or an absolute reduction of the SBP and DBP levels lower than 10/5 mmHg. Approximately 50% of the diabetic patients showed a non-dipper pattern of SBP and DBP (7 from the 13 patients showed a night reduction from SBP less than 10%, 6 in the case of DBP and 5 showed a night reduction of the SBP/DBP lower than 10/5 mmHg), versus lower than 14% of the healthy subjects (2 from 14 patients showed a night reduction of the SBP lower than 10%, and none of the healthy subjects showed a non-dipper pattern considering the two other used criteria). In the group of patients with diabetes, there was no difference in age, duration of diabetes or level of metabolic control, F.J. Vilchez López, et al.
control among the patients with dipper pattern and those with non-dipper pattern.\textsuperscript{37}

In the same year, Sivieri et al. carried out an ABMP to 17 patients with T1D, normal pressure and normal albuminuria and without autonomous neuropathy, and to a non-diabetic control group. Though the SBP and the DBP mean values during 24 hours were higher in the diabetic patients group, no relevant differences were found regarding to the variability of the 24 hours BP.\textsuperscript{38}

In 1996, Khan et al. detected a non-dipper pattern in 30.5\% or 41.6\% of the patients with T1D, normal pressure and normal albuminuria, versus 0.0\% or 13.0\% in the healthy control group, according to the criterion used (night decrease of BP lower than 10\% or an absolute reduction in the SBP/DBP levels lower than 10/5 mmHg, respectively). The changes in the BP variability were independent from the age, gender, HbA\textsubscript{1c} levels or isolated consultation BP.\textsuperscript{39}

Holl et al., in 1999, published a series of 354 adolescent patients with T1D and 1,121 healthy controls. The BP percentages in the different period were relevantly higher in the population with diabetes, in which the BP night reduction was, besides, lower (10\% versus 13\% regarding to the SBP, and 18\% versus 23\% regarding to the DBP), independent from the age. The authors did not detail the \textit{BHT} prevalence nor subclinical alterations of the BP (non-dipper phenomenon) in this population.\textsuperscript{40}

In 2001, Lurbe et al. compared the circadian BP pattern of patients with T1D and different levels of nephropathy and a group of healthy controls, including 57 subjects, 18\% showed a non-dipper pattern (defined as daytime DBP/night SBP lower than 1.07 or rate daytime DBP/night DBP lower than 1.12) and though this percentage was higher than in healthy controls (10\% non-dipper), the difference did not reach statistical significance.\textsuperscript{36}

Later, Darcan et al. diagnosed the BHT at 23.5\% of a pediatric series, when presenting the reading mean over the percentile 95 of BP for gender and age during a period of 24 hours (the 16.2\% were hypertensive during the daytime period and 32.4\% was at night). The 41.2\% showed a night reduction in the SBP or DBP lower than 10\% (non-dipper). In 16\% of the patients, micro-albuminuria was detected and in this group, non-dippers reached a prevalence of 63.6\%. There were no differences in the metabolic control level nor in the duration of the disease among the dipper and non-dipper patients.\textsuperscript{42}

Dost et al. informed in 2008 the results of the largest published series on this regard. They included 2,105 adolescents with T1D and 949 healthy controls. The mean pressures (SBP, mean BP [MBP] and DBP) both in the daytime period and at night were relevantly higher in the diabetic groups. Moreover, the night decrease of SBP and DBP was relevantly lower in this group compared with the controls (night reduction of SBP and DBP in patients versus controls, respectively: 10.00 ± 5.7 versus 13.0 ± 6.0\% and 16.8 ± 8.1 versus 23.0 ± 9.0\%, p <0.0001). Among the diabetic patients, 49.1\% showed a non-dipper systolic pattern and 17.5\% a diastolic non-dipper pattern (criterion: night SBP reduction and DBP <10\%, respectively). Persistent microalbuminuria was detected in 6.1\% of the diabetic patients, which is a factor associated to a diastolic non-dipper pattern in the multivariate analysis.\textsuperscript{35}

Table 4 sums up the results of the commented works in relation to the prevalence of the dipper/non-dipper pattern in patients with T1D.

\textbf{Prognosis implications}

The alterations in the \textit{BP} circadian rhythm in patients with T1D constitute an independent risk factor regardless of the onset of micro and macro-angiopathic complications:

- \textbf{Diabetic nephropathy.} Up to some years ago, it has been accepted that the \textit{BHT} in patients with T1D appeared as consequence of a renal affection, when there already existed an elimination of albumin in urine in pathological range. However, recent publications confirm that the onset of micro-albuminuria might be sec-

Review

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F.J. Vílchez López, et al.

Secondary to the previous alteration of the BP circadian rhythm.

Lurbe at al. carried out periodically a ABPM to a cohort of 75 patients with T1D, with normal pressure and normal albuminuria, during 5 years of follow-up. In this study, it was shown that previously to the onset of micro-albuminuria (that happened in 19% of the sample) an increase took place in the night SBP, while in the patients with normal albuminuria the levels of the night SBP at the end of the study remained stable, without changes as regards to the ones at the beginning of the follow-up. Thus, the increase of 5 mmHg in the night SBP increased significantly the micro-albuminuria risk (relative risk [RR]: 1.44) and in the same way, a final non-dipper pattern showed a positive predictive value of 31% for the development of micro-albuminuria, regardless of the glycemic control.

Lengyel et al., later, detected in the follow-up of 53 patients with T1D, normotensive and normal albuminuria that the development of micro-albuminuria (45%) was associated directly to the reduction of the daytime DBP/night DBP quotient, with higher levels of HbA1c, and the presence of retinopathy.

• Diabetic retinopathy. The BHT increases the risk of onset and progression of diabetic retinopathy in patient with T1D. The Renin-Angiotensin System Study included 194 patients with T1D, normal pressure and normal albuminuria, to whom a funduscopy and an ABPM were done. The 55% showed mild proliferative retinopathy and 13% serious-moderate non-proliferative diabetic retinopathy or proliferative. The seriousness of the retinopathy was positively correlated to the HbA1c levels and with the duration of the diabetes. Regardless of these variables, the night SBP levels were significantly higher in the group with higher retinopathy seriousness, 110 ± 9 mmHg in patients with retinopathy, 112 ± 9 mmHg in those with mild non proliferative retinopathy and 115 ± 9 mmHg in patients with serious non proliferative retinopathy or proliferative retinopathy (p= 0.002). The prevalence of the non-dipper pattern increased also in a parallel way to the seriousness of the retinopathy (19.28 and 36% respectively), though in this case the differences did not reach the statistical value (p= 0.08). In this study, the patients with night SBP among the 3 higher quartiles (≥103 mmHg) showed a higher risk of retinopathy compared to those with night SBP in the first quartile (OR: 3.71; confidence interval (CI) of 95%: 1.5-9.16; p= 0.004). These results match with the previous studies, that detect association between retinopathy and night DBP or retinopathy and SBP and night DBP.

• Macroangiopathic complications. We have not found prospective studies that evaluate the association between the circadian rhythm of altered BP and cardiovascular disease in patients with T1D, though we count with some data that suggest certain association between both. In this sense, Sturrock et al. published a retrospective study that included 75 patients with diabetes (41% with T1D), from which 50% were non-dippers. After a mean follow-up of 42 months, the cardiovascular mortality was higher in patients with altered circadian pattern (28 versus 8%). On the other hand, in a recently published study, which included 48 patients with T1D, normal pressure and normal albuminuria, aged 17 years and 8 years of diabetes evolution, it was demonstrated that the left ventricular mass was significantly higher among the non-dippers, as well as the ventricular diameters at the end of the systole and diastole.

Table 4. Prevalence studies of non-dipper pattern in patients with T1D

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Age (years)</th>
<th>Years of evolution</th>
<th>HbA1c (%)</th>
<th>Non “dipper” (%)</th>
<th>BHT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert et al.</td>
<td>13</td>
<td>38 ± 14</td>
<td>9.1 ± 5.5</td>
<td>7.8 ± 1.6b</td>
<td>Approx. 50c</td>
<td>–</td>
</tr>
<tr>
<td>Khan et al.</td>
<td>36</td>
<td>14.4 ± 2.1</td>
<td>4.0</td>
<td>8.6 ± 1.7a</td>
<td>30.5-41.6</td>
<td>–</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>28</td>
<td>27 ± 7.1</td>
<td>9 ± 6.6</td>
<td>8.9 ± 2.6a</td>
<td>78</td>
<td>–</td>
</tr>
<tr>
<td>Lurbe et al.</td>
<td>57</td>
<td>20.9 ± 10.5</td>
<td>6.4 ± 5.6</td>
<td>8.7 ± 1.9a</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>Darcan et al.</td>
<td>68</td>
<td>14 ± 4.2</td>
<td>5.7 ± 3.5</td>
<td>9.16 ± 1.25d</td>
<td>41.2</td>
<td>23.5</td>
</tr>
<tr>
<td>Dost et al.</td>
<td>2,105</td>
<td>14.05 ± 2.95</td>
<td>5.15 ± 4.02</td>
<td>8.0 ± 1.8b</td>
<td>17.5-49.1</td>
<td>–</td>
</tr>
</tbody>
</table>

*aHbA1c, timely measurement; bHbA1c, measured from the diagnosis (method used for the non-detailed estimation in the original study); capproximately 50%, according the used criterion.
Treatment
If the presence of a non-dipper pattern of BP increases the development and progression of the diabetes chronic complications, should we implement a treatment in the subjects with T1D clinically normotensive and normal albuminuria in which a circadian rhythm is detected of altered BP? We do not count with studies at long term and we have only found a study that evaluates the effect of the antihypertensive treatment in patients with T1D “clinically normotensive”, normal albuminuria, but with a non-dipper pattern of BP. Twenty-eight patients with T1D were included with the mentioned characteristics, being 18 of them treated with 2 mg/day oftrandolapril, and the effect with a ABPM was evaluated in all the cases. Considering the controls, in the patients treated pharmacologically it could be observed a relevant decrease of BP in both periods as from the treatment starting, as well as a more marked night decrease both in the SBP (from 3 to 17.6%; p <0.05) and the DBP (from 5.1 to 19.4%; p <0.05) after two weeks of treatment.53

Discussion
The BHT is a risk factor independent from the development and progression of the diabetes chronic complications.1,2 In spite of its relevance, there are only a few studies that have evaluated its prevalence in patients with T1D, as well as its control level.

With the data we count with at present, it is difficult to draw conclusions about the prevalence of the BHT in this population, considering that the results differ significantly in the different series. The main reasons are the use of different criteria about normality and the scarce homogeneity of the studied populations (table 3). Moreover, the prevalence in the different studies might be overestimated by two main reasons. First, because most of the studies use as BHT criterion the administration of hypotensive drugs, being likely that some patients with normal pressure shall undergo treatment with ACEI or ARA II for presenting microalbuminuria. Secondly, because the prevalence of the “physician phenomenon” (high isolated BP levels) is very high in the patients with T1D, reaching up to 75% in some series.54 Therefore, it would be interesting to count with studies of prevalence based on more reliable techniques, as the ABPM, though broad studies performed with this technique have not been found in the bibliographic revision.

On the other hand, the BHT control level has not been uniform either, though it is poor in most of the series. In the revised studies, less than 50% of the patients showed an adequate BHT control, except in the CACT1 study, where 55% of the patients showed BP values within the therapeutic target, probably because 83% was under hypotensive treatment, which is a quite high percentage compared to the rest of the studies.21

The ABPM is the unique technique that allows knowing the BP during the daily activity and during the sleep. In this sense, it provides information about the circadian rhythm of the BP, which in normal conditions decreased a 10% during the night period; a phenomenon known as BP dipper pattern.9 The non-dipper pattern is stressed by BP decreases lower than 10%, which is an entity that has been related to higher co morbidity in the patients with T1D. There are no conclusive data about the prevalence of this phenomenon in this population. The results of the different series are difficult to compare: the sizes of the different samples are frequently small and the characteristics of the populations are quite heterogeneous (table 4). Moreover, a main problem is the lack of uniformity in the definition of the non-dipper phenomenon. Except for The Hypertension Spanish Guideline, which bases the definition on the reduction of the mean BP,15 the rest of the guidelines do not specify if the BP variability should be considered in the MBP, in the SBP or in the DBP.16 The studies published on this regard in patients with T1D use different criteria: decrease of the night SBP lower than 10%,7 decreases of the SBP and the night DBP lower than 10%,37,47 decrease of the night SBP lower than 10% and the night DBP lower than 5%,36 or absolute night decrease of 10 mmHg for the SBP or 5 mmHg for the DBP.57 Regardless from the used criterion, the non-dipper pattern is significantly higher in patients with T1D compared to the general population of the same age and gender, not only among the patients with diabetic nephropathy,36,55-59 but also among patients with normal albuminuria.36,38-42 Khan et al. observed that 42% of the diabetic patients versus 13% of the healthy controls have a non-dipper pattern;39 for Cohen et al. these values were of 78% versus 43%.41 In the greatest series that has been published on this regard, which included 2,105 patients, it has been concluded that the night BP decrease was lower in the diabetic patients compared to the healthy controls, with relevant statistically differences.55
Publications arisen during the last years manifest the relevance of these subclinical alterations of the BP, that affect a not despicable percentage of patients with T1D and that usually pass unnoticed during the follow-up. The risk increase seems to be more consistent when considering the micro vascular complications. The group of Lurbe et al. demonstrated that the night increase of the SBP levels increase the risk of developing microalbuminuria significantly, regardless from the metabolic control of the diabetes. Moreover, both the frequency of the diabetic retinopathy and its seriousness are higher among patients with an altered circadian pattern. Finally, it seems that the presence of a non-dipper phenomenon also increases the cardiovascular risk, but the only study that we have found in this sense is retrospective and includes both patients with T1D and T2D. Therefore it would be necessary to conduct prospective studies and performed exclusively with patients with T1D in order to clarify this matter. In any case, recently published data suggest an early left ventricular failure among the patients with T1D with non-dipper pattern.

Considering the frequency of the non-dipper phenomenon in the patients with T1D, with normal pressure and normal albuminuria, and the increase of the complications risk that represent, is it convenient to treat these patients pharmacologically? The group of Czupryniak et al. demonstrated an early correction of the BP circadian rhythm when treating a group of patients with these characteristics with ACEI. However, we do not count with long term studies that prove the potential benefit of the hypotensive treatment in these patients, as regards to the risk of chronic complications, therefore it is necessary to perform intervention studies to show the efficiency of this measure.

Finally, the use of ABPM might identify susceptible patients on whom to intensify the follow-up or start an early treatment if they progress to BHT, but to present it is not known which patients should be benefited nor the periodicity that the ABPM should be carried out. The revised clinical studies include heterogeneous samples as regards to age, diabetes evolution time, metabolic control etc., without the non-dipper pattern has been related clearly with none of these variables. Probably, these matters shall be clarified in the future, as far as the ABPM is incorporated in a more generalized manner to the clinical attention of T1D patients.

Conclusions

At present, most of the evaluation and follow-up evaluation of patients with T1D incorporate the BP isolated measurement. However, this technique offers partial information; it presents a high variability, classifies wrongly the pressure status of some patients and does not reflect the presence of clinical alterations as important as the existence of a BP non-dipper pattern. This can be found altered in a high percentage of patients with T1D clinically “normotensive”, and constitutes a risk factor for the development and progression of chronic complications, mainly microangiopathic. It is a need to perform follow-up studies at long term to prove if the early anti hypertensive treatment in patients with BP subclinical alterations is translated into a decrease of the onset and progression of chronic complications in this population and, in that case, to design screening protocols of subsidiary patients of this measure.

Declaration of potential conflict of interests

F.J. Vilchez López, C. Coserria Sánchez, F. Carral Sanlaureano and M. Aguilar Diosdado state that there are no conflicts of interest as regards to the content of this article.
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