A Cross-Sectional Study Evaluating Orthostatic Hypotension in Normotensive and Hypertensive Patients with Diabetes Mellitus

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Abstract—Orthostatic Hypotension (OH) is a severe complication in diabetic patient. The objective of this cross-sectional study was to determine if OH is more prevalent in hypertensive diabetic patients than in normotensive diabetic patients and to investigate the relationship between the occurrence of OH and the duration of diabetes and/or Hypertension (HT).

Orthostatic Test was performed in 48 diabetic patients divided into two groups: Hypertensive Diabetic Patients (HDP) and Normotensive Diabetic Patients (NDP). Orthostatic Systolic Blood Pressure (ortho SBP) was recorded and compared to supine preorthostatic Systolic Blood Pressure (preortho SBP). To determine the prevalence of OH, three subgroups were selected from HDP and NDP groups as follow:

-Subgroup A : ortho SBP was higher than preortho SBP by 10 mmHg or more;
-Subgroup B : ortho SBP was lower than preortho SBP by 20 mmHg or more;
-Subgroup C: -20 mmHg<ortho SBP-preortho SBP<+10 mmHg.

The prevalence of OH was 42.3% in HDP vs 13.6% in NDP, p=0.029 in subgroup B.

In this study, the prevalence of OH was significantly higher in HDP than in NDP. Duration of HT and of diabetes in this study did not influence the prevalence of OH.

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Keywords — cardiac autonomic neuropathy, hypertension, orthostatic hypotension, systolic blood pressure, type 2 diabetes.

I. INTRODUCTION

Type 2 diabetes and Hypertension (HT) are two very prevalent disorders among adults that are known to be important risk factors for cardiovascular disease. They are so highly related that comorbidity is common1. The prevalence of HT in type 2 diabetes is more than 80%.2 The age-adjusted prevalence of HT increases with diabetes duration.3 Orthostatic Hypotension (OH) is one of the most striking features of cardiovascular involvement and the clinical hallmark of diabetic autonomic neuropathy4.

OH is defined as a reduction in the Systolic Blood Pressure (SBP) of at least 20 mmHg upon standing. OH is the inability to regulate BP within 3 minutes after moving from the Supine Position (SP) to the upright position.5 During this change in position, a lower input to the heart occurs due to the pooling of approximately 0.5 liters of blood in the lower extremities and pulmonary and splanchnic circulation.6 OH may be caused by both an abnormally large decrease in blood volume or by an inadequate cardio-vascular compensation from the decline in cardiac pre-load.6

Cardiac autonomic neuropathy (CAN) is a serious complication in diabetic patients. It should be suspected in the presence of an OH, frequently observed after several years of illness. Nevertheless, some studies suggest that CAN may occur earlier in the course of diabetes, even within the first 2 years following diagnosis7. The prevalence of CAN ranges between 60% and 75% of diabetic subjects8,9. Probably both reduced blood flow to nerves and endoneurial hypoxia explain the injuries of the peripheral nervous system10. The profile of CAN is mostly associated with an OH related to severe autonomic dysfunction11.

Few previous studies have focused on the impact of the association of HT and diabetes on autonomic nervous system (ANS)12,13. The objective of this study was to determine if OH is more prevalent in Hypertensive Diabetic Patients (HDP) than in Normotensive Diabetic Patients (NDP) and to investigate the
relationship between the occurrence of OH and the duration of diabetes and HT in the two groups.

II. METHODS

Patients
This cross-sectional study included 48 diabetic patients suffering from type 2 diabetes. The medical research ethics committee of the faculty of medicine of Rabat approved the study, and all patients involved provided a written consent form before being tested. Each patient completed also a form recording the presence or the absence of functional signs. According to association or not with HT, two groups were identified:

- **Group 1**: N = 26 HDP of which 46.2% were women, duration of diabetes was 72 months (48, 120) and duration of HT was 84 months (60, 120).
- **Group 2**: N = 22 NDP of which 68.2% were women, duration of diabetes was 68 months (36, 120).

Weight and height were measured to calculate the body mass index (BMI) of each subject using the usual formula weight / height², the result expressed in kg/m².

HT in diabetic patients was defined as systolic blood pressure (SBP) equal or higher than 130 mmHg and/or diastolic BP (DBP) equal or higher than 75 mmHg in the SP. Glycated hemoglobin A1c (HbA1c) was measured using capillary zone electrophoresis, performed on a Beckman Coulter P/ACE 5000 or P/ACE MDQ (Beckman Coulter, Fullerton, CA).

The two groups were matched for age (p = 0.23) and sex (p = 0.12), and we excluded all diabetic patients with degenerative complications of diabetes that could interfere with ANS involvement.

Orthostatic test
All recruited patients and control subjects underwent OT in the Center for Cardiac Autonomic Studies at the department of cardiology A, of the University Hospital Center (UHC) Ibn Sina, Rabat, Morocco.

The OT is a simple, non-invasive and reproducible test included among the cardiovascular ANS tests, involving the measurement of the Blood Pressure (BP) and the Heart Rate (HR) variation during the upright posture. The test was performed in the morning, after fasting and under no anti-hypertensive treatment during at least 48 hours except diabetic treatment.

The patient initially lied on a table of examination in a quiet room for at least 10 minutes. The monitoring of BP and HR was performed using a Dynamap (CRITIKON, 1846SXP) and a screen of posting (LCDCSS03E; HELLIGE, EK512E), respectively.

The basal systolic BP and HR were measured in both arms after a rest of at least 10 minutes. Then we proceeded to the OT. The orthostatic test was performed in two groups of diabetic patients: a group of HDP and a group of NDP. Orthostatic systolic BP (ortho SBP) was recorded for 10 minutes at the rhythm of 3 measurements per minute and compared with the values of supine systolic pre-orthostatic (preortho SBP).

To determine the prevalence of OH, three subgroups were selected from HDP and NDP groups as below:

**Subgroup A**: ortho SBP was higher than mean preortho SBP by 10 mmHg or more.

**Subgroup B**: ortho SBP was lower than mean preortho SBP by 20 mmHg or more.

**Subgroup C**: –20 mmHg < (ortho SBP – preortho SBP) < +10 mmHg.

OH was defined by a reduction in the systolic BP of at least 20 mmHg during the OT.

The OT is a cardiovascular autonomic test allowing the stimulation of the peripheral alpha sympathetic system by increasing the BP.

Duration of diabetes was collected in the two groups: HDP and NDP, duration of HT was collected in HDP group.

Besides comparing the prevalence of OH in the two groups, we also compared the severity of OH with the duration of both diabetes and HT.

Statistics
Descriptive statistics included the range, mean, and standard deviation for interval variables and the frequency and percentage for categorical variables. Group comparisons were carried out by independent samples Student’s t-test for interval variables and the χ² test for categorical variables, with the odds ratio (ORs) and 95% confidence intervals (CIs) calculated where appropriate. P values were 2 sided and were considered statistically significant if less than 0.05. All analyses were performed using SPSS, version 15.0 (SPSS Inc., Chicago, IL).

III. RESULTS

The mean age was 54.3 ±11.7 years in HDP (with extremes ranging from 36 to 75 years) vs 50.4 ± 10.4 years in NDP (with extremes ranging from 31 to 72 years), p = 0.23.

Mean basal HR did not differ significantly between the two groups (77.5 ± 15.2 beats/min in HDP vs 78.2 ± 14.9 beats/min in NDP, p = 0.9).

Mean basal SBP did not differ significantly between the two groups (150.3 ± 17.9 mmHg in HDP vs 113.1 ± 12.6 mmHg in NDP, p = 0.001) (Table 1).

Duration of diabetes was 72 months (48, 120) in HDP vs 68 months (36, 120) in NDP, p = 0.7.

Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HDP (n=26)</th>
<th>NDP (n=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>54.3±11.7</td>
<td>50.4±10.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>12/14</td>
<td>15/7</td>
<td>0.12</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>72 [48, 120]*</td>
<td>68 [36, 120]*</td>
<td>0.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.6 ± 1.4</td>
<td>8.2 ± 1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Duration of hypertension (months)</td>
<td>84 [60, 120]*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3±4.1</td>
<td>24.9±3.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Basal SBP (mmHg)</td>
<td>150.3±17.9</td>
<td>113.1±12.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal HR (beats/min)</td>
<td>77.5±15.2</td>
<td>78.2±14.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Values expressed as mean±SE. p significant if < 0.05. Student’s t-test.
HbA1c: Glycated hemoglobin A1c
BMI: Body mass index
SBP: Systolic blood pressure
HR: Heart rate

In sub-group B, mean preortho SBP was respectively 160.3 ± 19.7 mmHg in HDP vs 127.0 ± 1.7 mmHg in NDP. Mean orthostatic SBP was of 132.7 ± 22.1 mmHg in HDP vs 105.8 ± 5.3 mmHg in NDP (Table 2).

In HDP, duration of HT was of 108 months (48, 120) in HDP without OH, p = 0.8. In HDP, duration of HT was of 108 months (48, 120) in HDP with OH vs 84 month (60, 120) in HDP without OH, p = 0.8.

In sub-group A, mean preortho SBP was respectively 149.2 ± 19.7 mmHg in HDP vs 114.2 ± 14.8 mmHg in NDP. Mean orthostatic SBP was of 165.8 ± 26.1 mmHg in HDP vs 136.7 ± 9.7 mmHg in NDP (Table 2).

In sub-group C, mean preortho SBP was respectively 139.5 ± 7.2 mmHg in HDP vs 110.02 ± 11.7 mmHg in NDP. Mean orthostatic SBP was of 137.9 ± 10.3 mmHg in HDP vs 110.0 ± 12.1 mmHg in NDP (Table 2).

The prevalence of OH was then respectively 42.3 % in HDP vs 13.6% in NDP; p = 0.023 (Fig.1). In this subgroup, duration of diabetes was 120 months (48, 120) in HDP vs 120 months (84, 144) in NDP, p = 0.4.

The prevalence of orthostatic postural drop in BP was respectively 34.6% in HDP vs 63.6% in NDP; p = 0.045 (Fig.1).

Table 2

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>HDP</th>
<th>NDP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>preortho SBP</td>
<td>ortho SBP</td>
</tr>
<tr>
<td>A</td>
<td>149.2±19.7 (132-177)*</td>
<td>165.8±26.1 (136-200)*</td>
</tr>
<tr>
<td>B</td>
<td>160.3±19.7 (134-184)*</td>
<td>132.7±22.1 (99.5-162.4)*</td>
</tr>
<tr>
<td>C</td>
<td>139.5±7.2 (131-155)*</td>
<td>137.9±10.3 (135.5-142.7)*</td>
</tr>
</tbody>
</table>

Values expressed as mean±SE. Student’s t-test. Subgroups are defined in the Methods section.

*Results are given with extremes.

IV. DISCUSSION

The purpose of this study was to determine if OH is more prevalent in HDP than in NDP and to analyze if duration of diabetes, and HT had any influences on prevalence of OH (the severity of OH in these two groups). For that purpose, it was interesting to compare the peripheral Sympathetic Nervous System (SNS) response to stimulation in the two groups, using specifically OT as a cardiovascular autonomic test. In this study, OH was found in 11/26 patients (42.3%) in HDP, meanwhile 3/22 (13.6%) patients developed OH in NDP (p = 0.023). In an elegant study hypertensive diabetic patients had higher prevalence of orthostatic postural drop in BP as compared to normotensive diabetic patients. Masuo et al showed that OH was present in 20% of hypertensive patients and in 4% of normotensive subjects. The association of HT and type 2 diabetes is common. In this study, the prevalence of comorbidity with HT is found in 53.2% of diabetic patients.

OH may be caused by both an abnormally large decrease in blood volume or by an inadequate cardio-vascular compensation from the decline in cardiac pre-load and also by an inadequate sympathetic response.

Interestingly, Senard and al showed that the number of platelet alpha 2 adrenergic pairs is low in diabetic patients suffering from OH. Another study suggested that in diabetic patients with OH, the main site of the lesion is postsynaptic since alpha-adrenoreceptor coupling is altered. The profile of CAN is most often associated with an OH related to severe autonomic dysfunction. It has been suggested that there are considerable differences in the prevalence and associations of OH in different populations that are largely attributed to differences in population characteristics and methodology.
OH may involve both reduced blood flow to nerves and endoneurial hypoxia, perhaps causing the injuries of the peripheral nervous system\(^\text{10}\)\(^\text{10}\). The SNS plays a major role in maintaining BP during standing, through an increased release of neurotransmitters and the stimulation of postsynaptic adrenoreceptors\(^\text{10}\)\(^\text{10}\).

The mechanism of OH in HT patients suggests impaired baroreflex function in favor of central or peripheral neuropathy affecting the afferent and / or efferent ways\(^\text{10}\). In these situations, we observe a decrease in the secretion and / or abolition of the response of catecholamines in the upright posture\(^\text{10}\). Blomqvist demonstrated that OH is accompanied by a decrease in systolic ejection volume with increase in adrenergic tonic showed by increased catecholamines secretion responsible for vasoconstriction\(^\text{20}\). Masuo et al showed that basal supine plasma Norepinephrine (NE) was greater in hypertensive patients and in subjects with OH, and plasma NE response to upright posture is blunted in elderly hypertensive patients and in subjects with OH regardless of HT medications\(^\text{10}\). In our study, this higher prevalence of OH in HDP could be explained by the impact of duration of the association of HT with diabetes or of only the presence of HT in this population, because duration of diabetes did not differ significantly in our HDP and NDP groups. In HDP, duration of HT did not differ significantly between HDP with OH and HDP without OH, there is suggest that duration of HT no influenced the prevalence of OH, thus this higher prevalence of OH in HDP group could be explained by the impact of only the presence of HT with diabetes.

This difference in prevalence of OH in the 2 groups shows also the inadequate peripheral sympathetic response in HDP compared to NDP. Paolillo et al\(^\text{10}\) suggested that in aged diabetic subjects with a short duration of the disease - less than 5 years- and free from diabetic complications, it is possible to evidence a primary compromise of sympathetic rather than parasympathetic nervous system activity, since a greater rate of OH occurred. However, another study showed that autonomic neuropathy is related primarily to the involvement of the parasympathetic system\(^\text{18}\). The sympathetic system is involved later and leads to a very disabling dysautonomia\(^\text{22}\). In this study, in the HDP group, higher prevalence of OH could be explained by affecting the peripheral sympathetic system caused by the impact of the association of both HT and diabetes. Furthermore, the prevalence of no significant variation in orthostatic SBP differed significantly between the HDP and NDP groups, and showed a more stable variation of BP in NDP than HDP.

Possibly the presence of HT increases the inadequate peripheral sympathetic response in orthostasis in HDP. It would be interesting to conduct a further study focusing on a direct comparison including all the cardiovascular ANS tests between diabetic patients with and without HT. This is to our knowledge the first study focusing on comparison of ANS assessment between diabetic patients with HT and those without associated HT. Finally, applying a rigorous definition of impaired peripheral sympathetic activity has permitted us to highlight interesting differences in ANS response between diabetic patients with HT and those without associated HT.

V. CONCLUSIONS

HT in diabetic patients increases the risk of OH. Therefore, orthostatic testing in diabetic patients should be done routinely, especially in the presence of HT.

The duration of HT and of diabetes in this study did not influence the prevalence of OH. The mechanisms of ANS impairment in patients with HT and diabetic patients are likely complex and their study requires further and larger studies.

REFERENCES


