

Orthostatic Hypotension and associated factors in older adults Brazilian and French with diabetes

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Abstract— *Diabetic neuropathy is one of the major chronic complications of diabetes, including different clinical manifestations affecting the peripheral nervous system. The study aims to describe the characteristics of the older people with type 2 diabetes mellitus in Brazil and France who presented orthostatic hypotension and associated factors. This is a cross-sectional descriptive and analytical study, in which 248 Brazilian older adults with diabetes aged 65 or more and 987 older adults French with aged 75 or over, evaluated for the outcome of orthostatic hypotension, having the associated factors related to complications been analyzed. It was evident that 2/3 of the older adults Brazilian with diabetes 162 (69.8%) presented orthostatic hypotension on examination, while less than 1/3 of the French older adults with diabetes [301 (30.5%)] displayed this change on clinical examination, with statistically significant differences between the two populations for the variables: age, duration of diabetes, smoking, body mass index, degree of hypertension, diabetic neuropathy, amputations, obstructive limb arteriopathy, and use of antihypertensive drugs. The study reinforces the importance of tracking this important alteration of the physical examination, which may result in relevant chronic complication to the health of the older people with diabetes.*

I. INTRODUCTION

Brazil has been undergoing a process of demographic and epidemiological process with an increasing population of older people. In developed countries like France, the aging of the population took many years to come about, while in developing countries like Brazil, this demographic change occurred in one fifth of the period.¹

This global phenomenon experienced by several countries in different periods contributed to a higher prevalence of chronic non-communicable diseases (NCDs) such as cardiovascular diseases, neoplasia, chronic respiratory diseases, and diabetes *mellitus*. Among them,

diabetes stands out as the causes of high morbidity and mortality in Brazil, besides causing important economic repercussions.²

The World Health Organization (WHO) estimates that in 2030 Brazil will have a population of approximately 21.5 million diabetics,³ and that 33% of that population will be represented by people in the age group between 60 and 79.⁴ It is relevant to mention that the number of diabetics in the world population tends to increase, according to the following estimates: 463 million in 2019, 578 million in 2030 and 700 million in 2045.³

In France, an estimated 6% prevalence of diabetes is present in its general population, which is composed of a large number of older people at an average age of 65, mostly males (54%) and a significant percentage of immigrants (23%).—Diabetes mellitus (DM) is the most prevalent non-communicable chronic disease among all chronic conditions, responsible for doubling the rate of patients covered by the public health in that country over the past ten years.⁵

DM, as a chronic disease with high morbidity and mortality, results in numerous complications, both acute and chronic. Among the chronic ones, retinopathy, ischemic heart disease, neuropathies, nephropathy, cerebrovascular and peripheral vascular diseases stand out.⁶

In this context, diabetic neuropathy (DN) is the most prevalent chronic disease complication of DM, behaving as a heterogeneous group of clinical and subclinical manifestations that affect the peripheral nervous system (PNS) and its sensory motor and autonomic components.⁷ As diabetes evolves, there is an increased prevalence of diabetic neuropathy, which may exceed the figure of 50%.⁸

It is worth mentioning that 20% of the patients with DN will experience neuropathic pain, which is responsible for causing a significant reduction in the quality of life and the functional capacity. In addition, DN is a risk factor for complications such as deformities, ulcers, lower limb amputations and other microvascular changes.⁹ With the ample occurrence of diabetic neuropathy, there are three main forms of presentation: diffuse neuropathy, mononeuropathy and polyradiculopathy.⁷

The cardiovascular autonomic neuropathy (CAN) is defined as a set of abnormalities affecting the autonomic fibers that innervates the heart and blood vessels, causing changes in heart rate and vascular dynamics. The clinical manifestations resulting from these changes are resting tachycardia, exercise intolerance, orthostatic hypotension, syncope, intraoperative instability, silent myocardial infarction, ischemia and autonomic cardiomyopathy.¹⁰ When referring to CAN solely, there is an increase of its prevalence, which may reach 60-65%, depending on the time of the evolution of type 2 diabetes mellitus and the aging of the patient.^{7,10}

Orthostatic hypotension (OH) is defined by the pressure drop of ≥ 20 mmHg of the systolic blood pressure (SBP) or of ≥ 10 mmHg of the diastolic blood pressure (DBP) with a 3-minute interval between the initial position in supine position and the orthostatic position. Its pathophysiology can be summarized as a cardiovascular central and peripheral sympathetic denervation process, leading to failure in vasoconstriction of the vascular bed. It is also

known that the presence of orthostatic hypotension in a diabetic patient is associated with increased mortality in 10 years.^{11,12}

Orthostatic hypotension patients often experience dizziness, weakness, fatigue, blurred vision and cervical pain.¹³ The risk factors most associated with OH are: arterial hypertension, old age, antihypertensive drugs and diabetes mellitus.¹¹ The prevalence of OH in the world population is quite diverse and varies depending on the study performed, but is usually around 5% in younger patients aged 45-64 and averages 30% in older patients over 65 years old. This large variation or considerable range in prevalence is due to the different populations studied, considering which definition is being used and which technique is being applied to measure the blood pressure.¹⁴

Thus, the objective of this study was to describe the characteristics of the population of older people suffering from type 2 diabetes mellitus in Brazil and France, who presented orthostatic hypotension and associated factors.

II. MATERIALS AND METHODS

This was an international, cross-sectional, descriptive and analytical study. In Brazil, the research universe included 248 people aged 65 and over with diabetes type 2 mellitus (DM2), who had been diagnosed with this comorbidity for at least one year. They were selected by the original numbering of their medical records, one in every eight patients assisted by the specialized attention of the Unified Health System (SUS) of the Municipality of Fortaleza, capital of the State of Ceará. A comparison was made with the GERODIAB cohort of the Hospital Center of Rouen (CHU / Rouen) in the city of Rouen - France - where 987 diabetic older adults aged 70 and more were followed.¹⁵ The cutoff point used for the age in Brazil was 65 to equalize the samples between Brazil and France, since, in that country, the age of 70 was considered, which corresponds to five years more than the age considered for the French older adults.

The prospective, longitudinal, multicenter study called GERODIAB, was carried out in five geographic regions of France along five years, in which eligible individuals were recruited for follow-up and analysis of glycemic control and morbidity and mortality for DM2. The French specialized centers randomized for the follow-up of diabetic patients in the study were also part of a specialized network for the assistance of the older people in order to maintain the homogeneity of the patients' profile.¹⁶

The data were collected through a semi-structured questionnaire containing sociodemographic and clinical aspects related to diabetes mellitus (age, sex, time in years of illness, body mass index, waist/hip ratio, harmful habits); general health data (systemic complications, use of medications, arterial hypertension, orthostatic hypotension, among others). Concerning the clinical evaluation, the variables were identified from medical records taken by doctors at the specialized center, complemented with laboratory and imaging exams that participants of the study brought at the time of the clinical evaluation performed by the team responsible for the study in Brazil and France, identifying antecedents, associated diseases and developing complications of diabetes and treatment provided.

For the outcome of orthostatic hypotension (OH), during the clinical evaluation of the diabetic older adults, the pressure levels of the individual in the lying and standing positions were measured, in 1, 3 and 5 minutes after orthostasis with a manual sphygmomanometer properly calibrated. Orthostatic hypotension was defined as a reduction in systolic blood pressure (SBP) of at least 20 mmHg and/or a decrease in diastolic blood pressure (DBP) of at least 10 mmHg in any of the measurements in the standing position.¹⁷ The older people who were not able to undergo evaluation were excluded from the analysis of the study, totaling 16 of the total sample of Brazil.

The research project was approved by the Ethics Committee of the University of Fortaleza (Approval No. 1.666.717).

III. RESULTS

Of the total of the older adults with type 2 diabetes mellitus in the Brazilian sample ($n = 232$), 162 (69.8%) presented orthostatic hypotension on clinical evaluation, with no significant difference in age, sex, body mass index, presence of systemic artery hypertension, smoking, diabetic neuropathy, foot injury, amputation, obliterating arteriopathy of the lower limbs - OALL, coronary artery disease, heart failure and cerebrovascular disease (Table 1).

In the French sample ($n = 987$), 301 (30.5%) of the diabetic older adults included in the study had OH. There was a statistically significant difference between the Brazilian and French diabetic older adults in the following variables: average age in years ($p < 0.001$), time of disease in years ($p = 0.002$), body mass index ($p < 0.033$) (Table 2).

Concerning the comorbidity of systemic arterial hypertension, a statistical significance was observed in the

percentages of moderate to severe SAH among populations, with the highest frequency in the sample from France ($p = 0.001$). In relation to the average of pressure levels in the lying and standing positions in minutes 1, 3 and 5 in orthostasis, there is a statistically significant difference between lying DBP ($p < 0.001$), standing SBP in the first minute ($p = 0.008$) and DBP standing in the first, second and third minutes ($p < 0.001$) with higher averages in the Brazilian population in all of the variables cited (Table 3).

Among the chronic complications of type 2 diabetes mellitus, a greater frequency of peripheral neuropathy and amputation in Brazilians than in French was observed. ($p < 0.001$ e $p = 0.040$, respectively). Concerning obliterating arteriopathy of the lower limbs (OALL), the prevalence is higher for the French. ($p < 0.001$) (Table 4).

Table 5 shows a higher prevalence of older adults French with OH using inhibiting pharmacological class drugs of the angiotensin converter enzyme (ACE) ($p < 0.001$) beta-blockers ($p = 0.029$), diuretics ($p < 0.001$) and calcium channel antagonists (CCA) ($p < 0.001$) than the Brazilian older adults, with the exception of angiotensin receptor blockers (ARBs) (58.6% vs 40.9%) ($p < 0.001$) and the association of diuretics, CCA and other medications (15.4% vs 4.7%) ($p < 0.001$).

IV. DISCUSSION

From the total of 232 Brazilian diabetic older adults in study, 162 (69.8%) presented orthostatic hypotension (HO), while of the total of the French samples, ($n = 987$), 301 (30.5%) presented OH. Although the great difference in the prevalence of OH between the two populations is highlighted, this finding differs from the prevalence of 15.3% found in the literature of diabetic neuropathy, including orthostatic hypotension in the general population of people affected by DM2.¹⁸ However, the prevalence of OH ranges from 31 to 73% according to the diagnostic method; population studied and associated risk factors.¹⁹

In the Brazilian population, there was no statistically significant difference for gender, body mass index, smoking, coronary heart disease complications, heart failure and cerebrovascular disease and the presence of orthostatic hypotension, as in the American study of 302 older adults.²⁰

However, orthostatic hypotension has been associated with increased cardiovascular morbidity and mortality, especially for stroke and coronary disease.^{21,22,23}

The fact that there was a statistically significant difference between the Brazilian and French diabetic older adults who had OH on clinical examination for the

following variables: mean age ($p < 0,001$), average disease time in years ($p = 0.002$), body mass index ($p < 0,001$) and smoking ($p = 0.033$), is important.

It must be taken into account that the average age in the French sample may be greater by the inclusion criterion adopted as a cutoff point between the two populations, being 65 for Brazil and 70 France.

As for the time of diabetes mellitus in years, there was a greater mean time in the French sample. This difference can be related to the expected evolution of the disease with complications that would be more prevalent in a period of disease equal to or greater than 10 years, mainly in the age group of 60-69, considering that age and time of illness can be independent predictors for the clinical evolution of DM and orthostatic hypotension as its complication.^{18,24}

The activation of inflammatory cytokines plays an important role in the balance of the sympathetic system in diabetic patients, with inflammatory markers such as elevated CRP, IL-6 and TNF, exerting an inflammatory response in the adipose tissue.

However, the relationship between inflammation and diabetic neuropathy and orthostatic hypotension is uncertain and if it is bidirectional.^{10,19} This association, although not yet clear, may justify the association between obesity, comorbidity associated with chronic inflammation, and orthostatic hypotension in people carrying DM2.²⁵ There is a significant association between cardiac autonomic neuropathy in the diabetic patient and increased BMI. In addition, the prevalence of parasympathetic dysfunction is 25% in patients with obesity and autonomic cardiovascular neuropathy.²⁶

The findings detected a relative association to smoking and diabetic older adults ($p = 0.033$), as corroborated by authors who emphasize the evidence that there is a significant association between smoking and increased risk of developing DM2²⁷ and, even after 5 years of quitting, this risk remains elevated, decreasing only after 10 years of interruption.²⁸ When analyzing the association between smoking and the presence of microvascular complications such as diabetic neuropathy, two important studies have shown that this relation was significant in type 1 DM, but not in DM2.^{29,30} However, when with more sensitive and specific assessment of nerve conduction, smoking proved to be an independent risk factor for the manifestation of neuropathy in patients with DM2, especially in those with a greater smoking intensity, who presented worse nerve conduction.³¹

The research data showed that the mean pressure in the supine position for Brazilians were higher than for the French, with mean SBP ($p = 0.098$) and DBP ($p < 0,001$) respectively, which may be related to a higher prevalence

of OH in that population. Nevertheless, there was a higher percentage of moderate to severe hypertension in the French with orthostatic hypotension (91%; 274). Given this fact, it is worth mentioning that Systemic Arterial Hypertension (SAH) is a risk for OH, especially when referring to uncontrolled SAH ($BP \geq 140 \times 90$ mmHg) and systolic OH in the first minute, thus increasing the risk of falls.³² It is known that the incidence, when the two pathologies are associated, increases with age, probably due to altered autonomic and baroreflex functions, with baroreceptor sensitivity being reduced as the blood pressure level rises. There is evidence that the greater the blood pressure in the supine position, the greater the prevalence of OH in individuals over the age of 40.^{33,34} Although SAH occurs in more than 50% of adults with DM, there is little information on the incidence or prognosis of OH in this scenario.¹¹ The participants in the ACCORD study (2010) had a higher risk of OH because of DM, SAH and antihypertensive treatment. This was possibly due to the fact that patients undergo intensive treatment with antihypertensive drugs to obtain SBP < 120 mmHg, which contributes to an increased risk of OH due to the greater number and greater dosage of these medications.¹¹

Other studies show that OH was more prevalent in patients with not-controlled SAH and in the older adults, possibly due to side effects and the amount prescribed medication, which are based on the diagnosis of SAH performed by measuring the pressure level in the sitting position. Therefore, the systematic measurement of standing BP in all older adults with uncontrolled SAH is recommended, since more than 60% of the individuals studied with HO showed controlled levels of blood pressure when it was measured in orthostasis. In conclusion, if the BP measurement only in supine position is taken into account, a higher percentage of patients would need more aggressive treatment, which would probably worsen OH and its clinical consequences, such as syncope, falls, cardiovascular morbidity and mortality, functional impairment and hospitalization.²⁰

The study revealed a higher percentage of diabetic neuropathy ($p < 0,001$) and amputation ($p = 0.040$) in Brazilian diabetic older adults with OH than in French ones. This finding may be related to a higher prevalence of these complications in the Brazilian population compared to the French one. Additionally, the average time of the disease among French diabetics is higher than that of Brazilians and may present an indirect correlation with the orthostatic hypotension associated with this variable.²⁵ Conversely, the obliterating arteriopathy of lower limbs was more prevalent in French diabetic older adults with HO ($p < 0,001$), what can also be associated with the

highest percentage of this comorbidity in French older people.³⁵

This study found a higher percentage of the use of ACE inhibitors, beta-blockers, diuretics or calcium channel antagonists in the French diabetic older adults with orthostatic hypotension than in Brazilians, also corresponding to the classes of medication that have higher prevalence in France.³⁵ Therefore, we have that diabetic French older adults make more use of these medications and their use is associated with OH. For the use of Angiotensin Receptor Blockers (ARB), the research revealed an inverse association.

Although the association of antihypertensive drugs with orthostatic hypotension is controversial, with studies showing a reduced, similar or absent risk with this association,^{36,37,38,39,40} others show a positive association between this class of medication and the prevalence of OH. Among them, we highlight the beta-blockers, alpha-adrenergic receptor blockers and thiazides diuretics as the most frequently associated with OH,²⁵ while the ARBs do not show this relationship.^{21,41,42}

The mechanisms responsible for causing OH among antihypertensive drugs are decreased vasoconstriction, limited adjustment of the cardiac output and / or increased venous pool.⁴² It is important to mention that the dosages of the medications used were not taken into account in the analysis of the data.

Health professionals raise several concerns about the consequences of more intense treatment for BP reduction, despite all indications of therapeutic targets for hypertension in the literature.⁴³ These concerns led to warnings in recent guidelines on the initiation of anti-hypertension therapy in adults with a previous history of falls,^{44,45,46} once the physiological changes inherent to ageing, such as decreased baroreflex activity and loss of artery complacency become relevant factors when treating older hypertensive patients, as these changes lead to a greater risk of OH, consequently increasing the risk of falls and other complications. Furthermore, comprehensive studies mention the importance of knowing the real need to indicate a pharmacotherapy and to maintain SBP between 140 and 150 mmHg in order to avoid the emergence of the adverse events previously mentioned.^{47,48} Despite this, analyzes carried out later demonstrated that reducing BP more rigorously is not associated with OH.^{11,49}

The study is limited as we could not check for associations between the study variables and geriatric syndromes that can influence adherence to drug therapy and the presence for orthostatic hypotension among older adults with diabetes.

Due to the circumstances of the findings, the importance of systematization in the screening for orthostatic hypotension in diabetic individuals is emphasized, since the diabetic autonomic neuropathy is irreversible despite the numerous therapies established in the literature,²² affecting the treatment and prognosis of the diabetic patient.⁵⁰ It is no longer admissible that, during the evaluation of a diabetic older adults, blood pressure levels is not measured minimally in two positions, when possible.

V. TABLES

Table 1. Characteristics of diabetic older adults in Brazil with and without orthostatic hypotension (OH).

	OH Yes (n = 162)	OH No (n = 70)	P value
Age in years	73.2 ± 6.3	72.3 ± 5.8	0.375 ¹
Gender (female)	94 (58.0)	38 (54.3)	0.598 ²
Time of DM (in years)	14.5 ± 10.2	13.6 ± 8.6	0.903 ¹
BMI	28.4 ± 4.9	29.4 ± 5.2	0.393 ¹
Waist / hip	0.99 ± 0.07	0.99 ± 0.07	0.620 ¹
Smoker	14 (8.6)	6 (8.6)	0.986 ²
Arterial Hypertension	135 (83.3)	62 (88.6)	0.306 ²
Peripheral neuropathy	61 (41.2)	26 (39.4)	0.802 ¹
Foot wound	15 (9.3)	(7.1)	0.589 ¹
Amputation	10 (6.3)	3 (4.3)	0.759 ²
Obliterating arteriopathy of lower limbs (OALL)	13 (8.4)	4 (6.3)	0.783 ²
Coronary insufficiency	51 (31.9)	17 (24.3)	0.246 ¹
Heart Failure	18 (11.3)	13 (18.6)	0.140 ¹
Stroke	15 (9.3)	11 (15.7)	0.153 ¹

¹Mann-Whitney test; ²Chi-square test

Table 2. Comparison of demographic and anthropometric characteristics of Brazilian and French patients who presented Orthostatic Hypotension in the research.

	Brazil (n=162)	France (n=301)	P value
Age in years	73.2 ± 6.3	77±5	<0.001 ¹
Sex (female)	58.0	54.0	0.171 ²
Duration of disease in years	14.5 ± 10.2	17±11	0.002 ¹
BMI	28.4 ± 4.9	29.8±5.3	<0.001 ¹
Waist / hip	0.99 ± 0.07	0.98 ± 0.09	0.165 ¹
Smoker	14 (8.6)	5.0	0.033 ²

¹T test for a sample; ² Binomial test

Table 3. Pressure levels according to the assessment of orthostatic hypotension in Brazil and France.

	Brazil (n = 162)	France (n = 301)	P value
Arterial hypertension (moderate or severe)	135 (83.3)	274 (91.0)	0.001 ²
SBP lying down (mmHg)	149.2 ± 24.1	146 ± 21	0.098 ¹
Standing SBP (mmHg)			
1 min	139.0 ± 23.6	134 ± 23	0.008 ¹
3 min ¹	140.2 ± 23.7	137 ±	0.098 ¹
5 min	140.3 ± 23.7	137 ± 21	0.085 ¹
Lying DBP (mmHg)	84,3 ± 11,2	78 ± 11	<0,001 ¹
Standing DBP (mmHg)			
1 min	76,0 ± 11,6	71 ± 13	<0,001 ¹
3 min	76,3 ± 12,7	72 ± 12	<0,001 ¹
5 min	76,6 ± 11,9	72 ± 20	<0,001 ¹

¹T test for a sample; ² Binomial test

Table 4. Comparison between the older adults with OH, according to chronic complications related to diabetes mellitus.

	Brazil (n= 162)	France (n=301)	P value
Peripheral neuropathy	61(41,2)	26,2	<0,001 ²
Foot wound	15 (9,3) ²	7,0	0.158 ²
Amputation	10 (6,3)	3,3	0,040 ²
Obliterating arteriopathy of the lower limbs (OALL)	13 (8,4)	30,5	<0,001 ²
Coronary insufficiency	51 (31,9)	29,9	0.320 ²
Heart Failure	18 (11,3)	10,1	0.341 ²
Stroke	15 (9,3)	13,7	0.058 ²

Binomial test

Table 5. Comparison between diabetic older adults with OH regarding the classes of drugs used.

Class of medicines	Brazil (n = 162)	France (n = 301)	P value
ACE	23 (14,2)	37,2	<0,001 ²
ARB	95 (58,6)	40,9	<0,001 ²
Beta-blockers	54 (33,3)	40,9	0,029 ²
Diuretics	60 (37,0)	53,2	<0,001 ²
Calcium channel antagonists (CCA)	41 (25,3)	38,2	<0,001 ²
Diuretics + CCA	26 (16,0)	24,3	0,007 ²
Diuretics + CCA + other	25 (15,4)	4,7	<0,001 ²
Amount	1,7 ± 1,2	1,8 ± 1,0	0,224 ¹

¹T test for a sample; ² Binomial test

VI. CONCLUSION

A higher prevalence of orthostatic hypotension (OH) was detected in clinical evaluation among Brazilian older adults than in French ones. For OH, there was a significant difference between demographic and anthropometric characteristics such as average age in years; time of DM in years; body mass index and smoking. The pressure means in the supine position were higher for Brazilians, while there was a higher percentage of moderate to severe hypertension in the French.

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