Postural hypotension in type 1 diabetes: The influence of glycemic control and duration of illness

OA Oduwole[1,2], OF Adeniyi[1,2], CI Esezebor[1,2], E Ekure[1,2], IB Fajolu[1,2], JK Renner[1,2]

[1]Department of Paediatrics, College of Medicine, University of Lagos, [2]Lagos University Teaching Hospital, Lagos, Nigeria

Abstract

Background: Postural hypotension (PH) indicates the presence of cardiac autonomic neuropathy and in diabetes mellitus (DM) is associated with adverse outcome. Nonetheless, PH has been rarely characterized in young persons in Sub-saharan Africa where suboptimal care of DM is prevalent.
Aims: The aim of the study was to determine the prevalence of PH in young patients with type 1DM and its relationship with the duration of DM and glycemic control.
Settings and Design: It was a cross-sectional, case control study carried out in the pediatric out-patient clinic.
Materials and Methods: Each study participant had blood pressure (BP) measured in the supine and standing positions. Glycated hemoglobin (HbA1c) levels were determined and disease duration was documented.
Statistical Analysis: The mean BP in the different positions was determined. The occurrence of PH, duration of disease and HbA1c levels was determined with logistic regression analysis.
Results: A total of 26 diabetic subjects and 26 age and sex matched controls were studied. 12 (46.2%) diabetic subjects had evidence of PH while none of the controls had PH. Diabetic subjects with PH had significantly longer duration of DM than those diabetics without PH (6.79 ± 4.81 vs. 2.83 ± 2.36, P = 0.023). The mean HbA1c level was similar in both groups of diabetic subjects (9.79 ± 2.07 vs. 9.17 ± 2.35). On logistic regression, age, duration of disease, HbA1c level and body mass index were not significant predictors of PH.
Conclusion: PH is common in young persons with type 1 DM, with higher frequency in those with long standing disease.

Key words: Diabetes mellitus, duration, glycemic control, postural hypotension

Introduction

Postural hypotension (PH), which has been defined as a decrease in systolic blood pressure (SBP) ≥20 mmHg and or a decrease in diastolic blood pressure (BP) ≥10 mmHg, respectively within 3 min of standing is believed to be one of the dramatic clinical manifestation and hallmark of diabetic autonomic neuropathy.[1,2] It is believed to be one of the tests of sympathetic autonomic dysfunction that can be demonstrated in patients with diabetes mellitus (DM).[3] The phenomenon predicts significant adverse effects such as sudden death and renal failure.[4,5] I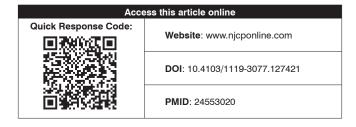n adults with DM, in whom PH has been well-characterized, it may reflect the impact of ageing, poor diabetic control or both and the prevalence has been reported to be between 3% and 35%.[6-8] Gyang et al.[9] while describing the complications of diabetes in a cohort of 283 diabetics (type 2 and type 1) in Jos, Nigeria documented prevalence of 3.9%. Eze et al.[10] on the other hand, noted that PH as detected by BP response to standing had the best positive predictive value of cardiac autonomic neuropathy (CAN) in the cohort of type 2 diabetics studied in Enugu.

Address for correspondence:
Dr. OF Adeniyi,
Department of Paediatrics, College of Medicine, University of Lagos, Lagos, Nigeria.
E-mail: layo_funke@yahoo.co.uk

On the other hand, in children, PH may relate to poor long term glycemic control with minimal effect of ageing.[8,11] In contrast to adults, few studies have characterized PH in children, in whom type 1 DM predominates.[6,11] Moreover, the few studies detailing PH in children were carried out in the developed regions of the world. Extrapolating these data to young persons with DM in developing countries of the world may be fraught with errors. One major reason for this is the suboptimal care many children in these countries receive; partly as a result of family poverty, competing needs at the household level and poorly resourced health facilities. Hence, these children are more likely to develop short- and long-term complications of DM including autonomic dysfunction. Thus, this study was aimed at determining the prevalence of PH and its associated risk factors among a cohort of young persons with DM.

Materials and Methods

A total of 26 consecutive patients with type 1 DM attending the Pediatric Diabetic Clinic of the Lagos University Teaching Hospital (LUTH) between July 2010 and February 2011 were the subjects for this study. The study was undertaken after ethical approval from the Health Research and Ethics Committee of LUTH was obtained. The caregiver of each subject or the subject (if 18 years or older) provided informed consent before enrolment in the study. All subjects were diagnosed with type I DM according to World Health Organization criteria[12] and received mixed insulin 70/30 twice-a-day. The subjects were also on twice daily monitoring of blood glucose at home and quarterly glycated hemoglobin (HbAIc) monitoring. Apparently healthy age and sex matched controls without any known structural heart disease, metabolic or chronic disease or acute illness, with normal blood glucose (70-110 mg/dl) and HbA1c (4.5-6.5%) were also recruited. Subjects with any acute illness (including febrile illnesses, diabetic ketoacidosis and gastroenteritis), a known structural heart disease and those on any antihypertensive were excluded.

This study focused on determining PH with change in the BP with posture which basically reflects sympathetic autonomic dysfunction. Each study participant had their weight and height measured during a routine clinic visit and the body mass index (BMI) was determined. After remaining calm and supine on an examining couch for 5 min, BP was taken on the right hand using a mercury sphygmomanometer with an appropriate cuff as recommended by the Fourth Report on the diagnosis, evaluation and treatment of high blood pressure (BP) in children and adolescents.[13] Thereafter, the subject was asked to stand for 3 min and then the BP measurement repeated. The mercury levels at the first and fifth Korotkoff sounds were taken as the systolic and diastolic BP. Two BP measurements were taken in the supine and also in the standing position and the average of the readings was taken as the BP for each position. The BP was measured twice when supine and when standing and the average of the two readings was used to determine the presence of PH.

Definition of terms
Normal BP was defined as SBP and diastolic blood pressure (DBP) values less than 90th percentile for the child's age, sex and height.[13]

PH was defined as a decrease in SBP ≥ 20 mmHg and/or a decrease in diastolic BP ≥ 10 mmHg.[6]

Hypertension was defined as BP >95th centile for age, sex and height.[13]

Determination of microalbuminuria and glycated hemoglobin
Urine and blood samples were collected from each subject for determination of microalbuminuria and HbA1c levels respectively.

Microalbuminuria was determined by dipping a micral strip into freshly collected urine sample and read using a visual analog scale. The glycated HbA1c was measured using the Clover A1C Analyzer, which uses the reflectance spectrophotometer method.

Statistical analysis
Categorical and continuous data were summarized as proportions and mean (SD) respectively. Chi-square test was used to test the differences between categorical data and student *t* test was used for continuous data. Logistic regression analysis was used to identify predictors of PH. In all statistical tests, a $P < 0.05$ in two tails was considered significant.

Results

The study population comprised of 26 subjects and 26 aged and sex matched controls.

Table 1 shows the clinical characteristics of subjects with diabetes and non-diabetic controls. Subjects with diabetes had significantly higher diastolic BPs both in the supine ($P = 0.001$) and standing positions ($P = 0.013$). However, there were no significant differences between subjects with diabetes and control subjects in age, sex and BMI.

The mean duration of DM was 5.0 ± 4.3 years and the mean HbA1c level was 9.5 ± 2.2% in the diabetic subjects. Postural hypertension was observed in 12 (46.15%) of the diabetic subjects. Two of the diabetic subjects were hypertensive and one of these also had PH. However, none of the controls had PH.

Comparison of subjects with PH and without PH

Table 2 shows a comparison of the study participants with and without hypotension. The diabetic subjects with hypotension had a statistically significant longer duration of illness (*P* = 0.023) than those diabetics without PH. Similarly, the mean SBP in the supine position (117.2 ± 4 versus 111.04 ± 11.3) and standing position (115.7 ± 14.7 versus 103.0 ± 8.1) were significantly higher in the diabetic subjects with hypotension than those without (*P* = 0.023 and *P* = 0.035 respectively). The diastolic BP was however similar in both groups.

The mean HbA1c was similar in the diabetic subjects with and without PH. The urinary albumin level was higher in the group with PH, but this did not reach statistical significance level (31.7 ± 27.6 versus 17.1 ± 23.6).

Relationship between PH, glycemic control and duration of illness

Table 3 shows a comparison of duration of illness and glycated HbA1c levels in the diabetic subjects with and

without PH, 8 (66.7%) of the 12 subjects with PH had HbA1c levels greater than 9% with significantly poor metabolic control. 9 (75%) of the subjects with PH also had a duration of illness longer than 5 years. The duration of illness was also significantly related to the occurrence of PH (Chi-square value = 4.013, *P* = 0.043).

Predictors of PH [Table 4]

None of the parameters (i.e., Age, BMI, Duration of DM, HbA1c) tested was able to significantly predict PH in this cohort of diabetic subjects.

Discussion

Our study shows a high prevalence of PH (41.5%) among young persons with DM compared with the non-diabetic subjects who did not have any evidence of PH.

This prevalence is significantly higher than those reported in studies of persons with type 1 DM.[4,14,15] it is however to be noted that the highest prevalence of PH has been observed amongst hospitalized individuals (52-69%) and the lowest among community-dwelling individuals (5-30%).[16,17] The wide differences in the reported prevalence of PH may be partly explained by the differences in the study population and definition of PH. To minimize this we adopted the recent consensus on the definition of PH as a drop in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic within 3 min of either standing or head-up tilt of at least 60°.[6,18] This may have contributed to the higher prevalence of PH in the present study. A higher prevalence has also been observed by other researchers when the standing BP is taken 3 min after standing compared to when the BP is taken 1 min after standing.[4] BP changes to posture has been observed to be a reliable indicator of sympathetic autonomic dysfunction even in diabetic patients.[10] Other workers have demonstrated the presence of PH with heart rate variability, but this was not evaluated in this study.

Table 1: Clinical characteristics of the study participants			
Parameters	Diabetic subjects (*n*=26; 100%)	Controls (*n*=26; 100%)	*P* value
Age (years)	13.2±5.3	11.2±6.0	0.222
Sex	M (16), F (10)	M (16), F (10)	-
BMI (kg/m²)	19.9±3.4	18.3±2.3	0.443
Duration of DM (years)	5.0±4.3	-	-
Supine SBP (mmHg)	110.2±12.9	104.5±8.0	0.070
Supine DBP (mmHg)	74.6±10.9	65.8±6.0	0.001
Standing SBP (mmHg)	109.5±13.3	103.1±10.6	0.081
Standing DBP (mmHg)	73.4±20.2	66.73±7.8	0.013
HbA1C (%)	9.5±2.2	-	-

Continuous data are mean±SD unless otherwise stated. *P* values are for the difference between the diabetic subjects and the controls. Blood sugar-Mean monthly fasting blood sugar. SPB=Systolic blood pressure; DPB=Diastolic blood pressure; HbA1c=Glycated hemoglobin; DM=Diabetes mellitus; BMI=Body mass index

Table 2: Comparison of clinical and laboratory features of study participants with and without hypotension					
Parameters	Diabetic PH (*n*=12; 46.2%)	Subjects no PH (*n*=14; 53.8%)	*P* value	Controls PH (*n*=0; 0%)	No PH (*n*=26; 100%)
Age (years)	14.7±4.9	11.4±5.4	0.12	-	11.2±6.0
Sex	M (5), F (7)	M (11), F (3)	-	-	M (16), F (10)
BMI (kg/m²)	20.3±3.6	19.3±3.7	0.53	-	19.8±2.3
Duration of DM (years)	6.8±4.8	2.8±2.4	0.02	-	-
Supine SBP (mmHg)	117.2±11.4	104.3±11.3	0.02	-	104.5±8.0
Supine DBP (mmHg)	77.4±10.8	72.0±11.4	0.30	-	65.8±6.0
Standing SBP (mmHg)	115.7±14.7	103.0±8.1	0.04	-	103.1±10.6
Standing DBP (mmHg)	81.2±10.5	60.8±28.1	0.05	-	66.73±7.8
HbA1C (%)	9.8±2.1	9.2±2.4	0.53	-	-
Blood sugar (mg/dl)	123.33±8.22	116.14±9.55	0.05	-	-
Urinary albumin (mg/dl)	31.7±27.6	17.1±23.6	0.26	-	-

Continuous data are mean±SD unless otherwise stated. *P* values are for the difference between the diabetic subjects with and without postural hypotension. Blood sugar-Mean monthly fasting blood sugar. SPB=Systolic blood pressure; DPB=Diastolic blood pressure; HbA1c=Glycated hemoglobin; PH=Postural hypotension; DM=Diabetes mellitus; BMI=Body mass index

Table 3: Glycated hemoglobin levels and duration of illness in diabetic subjects with and without postural hypotension

Parameters	PH *n* (%) 12 (100)	No PH *n* (%) 14 (100)	Total *n* (%) 26 (100)	*P* value
HbA1c (%)				
<6.5	0 (0)	1 (7.2)	1 (3.8)	0.057
6.5-9	4 (33.3)	10 (71.4)	14 (53.8)	
>9	8 (66.7)	3 (21.4)	11 (42.4)	
Duration of illness				
<5 years	3 (25)	11 (78.6)	14 (53.8)	0.043
>5 years	9 (75)	3 (21.4)	12 (46.2)	

PH=Postural hypotension; HbA1c=Glycated hemoglobin levels

Table 4: Multiple regression analysis showing independent predictors of postural hypotension in diabetes subjects

Parameter	OR (95% CI)	*P* value
Age (year)	0.96 (0.63-1.47)	0.88
BMI (kg/m²)	1.07 (0.36-3.16)	0.90
Duration of DM	0.58 (0.17-1.99)	0.39
HbA1c (%)	0.61 (0.11-3.31)	0.57
Blood sugar (mg/dl)	0.80 (0.62-1.03)	0.09

OR (95% CI) refers to odds ratio (95% confidence interval values), *P* <0.05 are considered as significant. Blood sugar-Mean monthly fasting blood sugar. BMI=Body mass index; DM=Diabetes mellitus; HbA1c=Glycated hemoglobin; CI=Confidence interval; OR=Odds ratio

The absence of PH in the controls in this study may not be entirely surprising as this phenomenon is not a common occurrence in normal children compared to adults where the presence of PH has been explained by ageing, drugs and other adult onset neuropathies.

The poor glycemic control observed in the cohort in this study may also explain the high prevalence of PH observed. The mean HbA1c and fasting glucose level of 9.5% and 120 mg% respectively underscores this observation. The similarity between the mean HbA1c in the diabetic subjects with PH and without PH may suggest the lack of an association between PH and mean HbA1c. However, the mean HbA1c for the cohort was high, thus when the subjects were grouped according to the presence or absence of PH the positive/significant effect of HbA1c on PH was not apparent. Although, the study did not explore reasons for poor glycemic control, non-adherence to life-style modification measures and insulin therapy commonly explain it. In a developing country, such as Nigeria non-adherence is aggravated by family poverty, self and family denial of disease and ignorance about the nature of DM. The vast majority of the subjects in this study being adolescents may also have explained the poor glycemic control. In general, adolescence represents a vulnerable period for non-adherence to treatment plans and a period when significant adverse outcomes occur in persons with chronic illnesses such as DM and chronic renal failure.[19]

Long standing poor glycemic control pre-disposes patients to microvascular complications and autonomic neuropathy, of which PH is one.[20-22] This results from damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature.[23] In addition, there is a decrease in cutaneous, splanchni and total vascular resistance that occurs in the pathogenesis of this disorder.[24] PH may therefore serve as a marker of autonomic neuropathy in this cohort of patients. Similar observations on poor glycemic control and the occurrence of CAN has been documented by Odusan *et al*.[25] in type 2 diabetics in Nigeria. It is important to note that the diabetic in our study were asymptomatic as none complained of the known symptoms of PH. Such symptoms are dizziness, weakness, fatigue, visual blurring and neck pain. This is not unusual as adults who have a longer duration of diabetes usually remain asymptomatic despite significant falls in blood pressure.[26]

Long standing DM was also observed to be significantly associated with PH in our study. The subjects with PH had a longer duration of diabetes compared with those without PH (6.79 ± 4.81, vs. 2.83 ± 2.36 years, *P* = 0.023). It was also observed that 9 (75%) of the subjects with PH actually had duration of disease above 5 years. There is increased likelihood of poorer adherence with longer duration of illness. It is a known fact that diabetes with duration above 5 years is more associated with complications especially when this occurs with poor metabolic control. In addition, the longer the duration of DM, the more likely that the impact of poor glycaemic control will reflect as clinically recognizable complications.[6]

PH in diabetes has also been linked to the presence of microalbuminuria and other microvascular complications.[27-28] However, in our study, the positive relationship between PH and microalbuminuria was weak. Like PH and retinopathy, microalbuminuria indicates the presence of microvascular damage in persons with DM and being an early predictor of kidney damage represents an important screening tool in reducing renal complications of DM. However, when the parameters were put to multiple logistic regression analysis none could independently predict the occurrence of PH, indicating the possible presence of some unexplored predictors of PH in the study. The reason for this is not clear, but could be explained by the small number of subjects in the study.

In this study, the SBP readings in the supine and standing position were significantly higher in subjects with PH than those without PH and this observation has also been made by other workers.[4,19,26] The reason for this however remains unclear and this occurrence may due to individual idiosyncrasy or peculiarities. However, the presence of both elevated SBP and PH in the same individual makes treatment of hypertension difficult as such measures worsen the magnitude of the PH.

Limitations

Our study has some limitations; one is the small sample size, which limits extrapolation of the findings; however, our clinic is one of the largest in Nigeria and all eligible subjects were recruited. The use of the Tilt table to determine the presence of PH was not possible in the study due to its unavailability. It would have been desirable to repeat the BP readings in the study cohort, but some had been lost to follow-up and thus the persistence of PH could not be ascertained. Presence of PH over several days may carry more significant clinical implications.

Conclusion

This study documents a high prevalence of PH among young persons with DM in Nigeria. The mean HbA1c level indicates a poor glycemic control among our population of children with DM; thus, measures targeted at improving diabetic care should be emphasized. PH was strongly related to the duration of DM.

Acknowledgment

The authors would like to thank Dr. Rita Maduako and other resident doctors in pediatrics for their help in data collection and recruiting of the study participants.

References

1. Wood JR, O'Riordan MA, Vogt BA, Palmert MR. Blood pressure measurement in diabetes clinic: Are we paying enough attention? Diabetes Care 2006;29:743-4.
2. Low PA. Prevalence of orthostatic hypotension. Clin Auton Res 2008;18:8-13.
3. Elamin A, Rajesh K, Tuvemo T. Cardiac autonomic dysfunction in children and adolescents with type 1 DM. Sudan JMS 2007;2:95-8.
4. Hirai FE, Moss SE, Klein BE, Klein R. Postural blood pressure changes and associated factors in long-term Type 1 diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy. J Diabetes Complications 2009;23:83-8.
5. Klein BE, Klein R, McBride PE, Cruickshanks KJ, Palta M, Knudtson MD, *et al.* Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. Arch Intern Med 2004;164:1917-24.
6. Winkler AS, Bosman DR. Symptomatic postural hypotension in diabetes: Aetiology and management. Pract Diabetes Int 2003;20:219-25.
7. Luukinen H, Airaksinen KE. Orthostatic hypotension predicts vascular death in older diabetic patients. Diabetes Res Clin Pract 2005;67:163-6.
8. Gottsäter A, Ahmed M, Fernlund P, Sundkvist G. Autonomic neuropathy in Type 2 diabetic patients is associated with hyperinsulinaemia and hypertriglyceridaemia. Diabet Med 1999;16:49-54.
9. Gyang SS, Wannang NN, Sokomba EN. Prevalence and treatment of diabetic complications in patients attending the diabetic clinic of plateau specialist hospital, Jos, Nigeria: A retrospective study. Niger J Pharm Res 2005; 4:39-45.
10. Eze C, Onwuekwe I, Ogunniyi A. The frequency and pattern of cardiac autonomic neuropathy (CAN) in type 2 DM patients in a diabetic clinic in Enugu South-East Nigeria. Niger J Med 2013;22:24-31.
11. Kempler P, Tesfaye S, Chaturvedi N, Stevens LK, Webb DJ, Eaton S, *et al.* Blood pressure response to standing in the diagnosis of autonomic neuropathy: The Eurodiab IDDM Complications Study. Arch Physiol Biochem 2001;109:215-22.
12. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO Consultation. World Health Organization Department of Non communicable Disease Surveillance Geneva: WHO;1999.
13. Fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents: a working group report from the national blood pressure education program. Paediatr 2004;114:555-6.
14. Salawu FK, Danburam A, Olokoba AB. Non-motor symptoms of Parkinson's disease: Diagnosis and management. Niger J Med 2010;19:126-31.
15. Vinik AI, Erbas T. Recognizing and treating diabetic autonomic neuropathy. Cleve Clin J Med 2001;68:928-30, 932, 934.
16. Alagiakrishnan K. Approach to management of postural hypotension. Geriatr Aging 2007;10:298-304.
17. Shafiq R, Rashid A, Aamir AH. Prevalence of orthostatic hypotension among diabeticpatients in a community hospital of Peshawar, Shafiq ur Rahman. Pak J Physiol 2010;6:37-9.
18. American autonomic society and the American academy of neurology. Consensusstatement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. In: Robertson D, Low PA, Polinsky RJ, editors. Primer on the Autonomic Nervous system. San Diego: Academic Press;1996. p. 334-6.
19. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation 2007;115:387-97.
20. Wahid ST, Baines LA, Savopoulos L, Connolly VM, Kelly WF, Bilous RW. Longitudinal analysis of blood pressure, lipid, and glycemic control in diabetic patients with nephropathy attending a hospital outpatient clinic and their relationship to renal function, mortality, and cardiovascular morbidity. Diabetes Care 2001;24:789-90.
21. Skyler JS. Effects of glycemic control on diabetes complications and on the prevention of diabetes. Clinical Diabetes 2004;22:162-6.
22. Torchinsky MY, Gomez R, Rao J, Vargas A, Mercante DE, Chalew SA. Poor glycemic control is associated with increased diastolic blood pressure and heart rate in children with Type 1 diabetes. J Diabetes Complications 2004; 18:220-3.
23. Low PA, Benrud-Larson LM, Sletten DM, Opfer-Gehrking TL, Weigand SD, O'Brien PC, *et al.* Autonomic symptoms and diabetic neuropathy: A population-based study. Diabetes Care 2004;27:2942-7.
24. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553-79.
25. Odusan O, Familoni OB, Raimi TH. Correlates of cardiac autonomic neuropathy in Nigerian patients with type 2 diabetes mellitus. Afr J Med Med Sci 2008;37:315-20.
26. Pop-Busui R. Cardiac autonomic neuropathy in diabetes: A clinical perspective. Diabetes Care 2010;33:434-41.
27. Jermendy G. Clinical consequences of cardiovascular autonomic neuropathy in diabetic patients. Acta Diabetol 2003;40 Suppl 2:S370-4.
28. Lafferty AR, Werther GA, Clarke CF. Ambulatory blood pressure, microalbuminuria, and autonomic neuropathy in adolescents with type 1 diabetes. Diabetes Care 2000;23:533-8.