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FinnDiane Study Grp

2020-08

FinnDiane Study Grp , Eriksson , M I , Gordin , D , Shams , S , Forsblom , C , Summanen , P , Liebkind , R , Tatlisumak , T , Putaala , J , Groop , P-H , Martola , J & Thorn , L M 2020 , ' Nocturnal Blood Pressure Is Associated With Cerebral Small-Vessel Disease in Type 1 Diabetes ' , Diabetes Care , vol. 43 , no. 8 , pp. E96-E98 . https://doi.org/10.2337/dc20-0473

http://hdl.handle.net/10138/322441
https://doi.org/10.2337/dc20-0473

acceptedVersion

Nocturnal blood pressure is associated with cerebral small-vessel disease in type 1 diabetes

Short running title: Blood pressure in cerebral small-vessel disease

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Word count: 745 Tables: 1 Figures: 0

Although vascular complications are a hallmark of diabetes, cerebral small-vessel disease (cSVD) in type 1 diabetes remains scarcely studied. We recently showed that cSVD is more common in individuals with type 1 diabetes than healthy controls and is associated with systolic office blood pressure (BP) (1). Hence, we aimed to further evaluate the impact of BP on cSVD in type 1 diabetes.

Methods. This substudy of the Finnish Diabetic Nephropathy Study aims to assess early markers of cerebrovascular disease in people with type 1 diabetes, and has previously been described in detail (1). Of the 191 neurologically asymptomatic study participants, 73 volunteered for a 24-hour ambulatory BP monitoring (ABPM). All participants underwent a clinical study visit and brain MRI assessed for markers of cSVD (white-matter hyperintensities, lacunar infarcts, and cerebral microbleeds) (1, 2).

The 24-hour ABPM was conducted in accordance with current standards (3). After ABPM-quality validation, we calculated average BP, mean arterial pressure (2/3 diastolic + 1/3 systolic BP), pulse pressure (PP, systolic - diastolic BP), BP variability (average real variability) and nocturnal dipping ([1-nocturnal systolic/ diurnal systolic BP] x 100%). Elevated BP and masked hypertension were defined as described by the European Society of Hypertension (3).

Results. We observed cSVD in 20 (27.4%) participants, of whom 14 had cerebral microbleeds, nine white-matter hyperintensities, and two lacunes. Table 1 includes clinical characteristics as well as main results for BP measurements based on presence or absence of cSVD. In addition, participants with cSVD had more often nocturnal hypertension (12 [60.0%] vs. 16 [32.0%], p=0.031) that was independently associated with cSVD (OR=4.09 [95% CI 1.27–13.2], p=0.019) after adjustment for age, antihypertensive medication, and ABPM-quality. The same

was true for masked hypertension (10 [50.0%] vs. 12 [25.0%], p=0.030 and OR=3.74 [95% CI 1.17–12.0], p=0.020). No association was seen for elevated office BP, diurnal BP, or 24-hour BP (data not shown).

Our findings were more prominent in participants on antihypertensive therapy, in whom participants with cSVD had higher systolic BP (127 [119-132] vs. 113 [108-117] mmHg, p=0.001), diastolic BP (75 [70-78] vs. 67 [64-73] mmHg, p=0.021), and a higher prevalence of nocturnal and masked hypertension (7 [78.5%] vs. 7 [35.0%], p=0.033 and 6 [75.0%] vs. 5 [23.8%], p=0.028, respectively). In participants without antihypertensive medication, BP did not differ between those with or without cSVD.

Conclusion. This study indicates a link between nocturnal BP and asymptomatic microvascular disease of the brain in type 1 diabetes. As novel findings, we show that higher nocturnal systolic and diastolic BP, mean arterial pressure, as well as nocturnal and masked hypertension are associated with cSVD in type 1 diabetes. To this date, this is the only existing study on ABPM and brain MRI in type 1 diabetes.

In healthy elderly people, an association between increased ABPM and cSVD, has previously been observed (4). In accordance with our results, this study showed an association between higher nocturnal BP and cSVD, and furthermore, that elevated diurnal and 24-hour BP were associated with cSVD. These discrepancies could be due to the difference in age, BP levels, or the use of antihypertensive medication between the study cohorts. Nocturnal BP is, however, recognized as a stronger predictor of cardiovascular events than diurnal BP (3). Our results indicate that elevated nocturnal BP is associated with early markers of cerebrovascular disease.

We observed no association between cSVD and PP, a marker of arterial stiffness. In type 1 diabetes, arterial stiffness has been associated with cerebral white-matter hyperintensities, a marker of cSVD (5). In our younger cohort, white-matter hyperintensities were too infrequent for any further subanalyses. The different manifestations of cSVD (2) could potentially have different pathophysiology, and, thus, also differ in their association with BP.

We observed more prominent findings in individuals on antihypertensive medication. No association was, however, found between cSVD and antihypertensive medication, as opposed to earlier observations (4). This may indicate that a higher nocturnal BP is a marker of a pre-existing generalized circulatory dysregulation, or it may be due to taking BP lowering medication during daytime.

The study limitations include the lack of power to detect more subtle differences between the groups and the cross-sectional design that limits the interpretation of causality. Nonetheless, the strength of our study is the well-characterized study population and the detailed evaluation of both BP and cSVD.

Our findings show that cSVD in type 1 diabetes is associated with nocturnal BP and masked hypertension. Whether the link is causal, or simply reflect vasculopathy and/or BP dysregulation needs further investigation.

Acknowledgements

We acknowledge the skilled technical assistance of Anna Sandelin, Jaana Tuomikangas, and Mira Korolainen. We also gratefully thank Pentti Pölönen, Department of Radiology, Helsinki University Hospital for performing the MRI scans. We are indebted to Prof. Markku Kaste,

Department of Neurology and Dr Oili Salonen, Department of Radiology, Helsinki University Hospital for their help in the initiation of the study.

M.I.E., D.G., S.S., C.F., P.S., R.L., T.T., J.P., P.-H.G., J.M. and L.M.T. contributed to the study design, acquisition of data, as well as the interpretation of data. M.I.E. and L.M.T. had the main responsibility for analyzing the data and writing the first draft of the paper. D.G., S.S., C.F., P.S., R.L., T.T., J.P., P.-H.G. and J.M. critically revised the manuscript. P.-H.G. is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding. The study was supported by grants from Folkhälsan Research Foundation, Academy of Finland (275614, 316664, and UAK10121MRI), Wilhelm and Else Stockmann Foundation, Liv och Hälsa Society, Novo Nordisk Foundation (NNF OC0013659), Sigrid Juselius Foundation, Medical Society of Finland, Päivikki and Sakari Sohlberg Foundation, Finnish Foundation for Cardiovascular Research, EVO governmental grants, University of Helsinki, Diabetes Research Foundation, Diabetes Wellness Finland, Finnish Medical Foundation, Perklén Foundation, Eye Foundation in Finland, and Eye- and Tissue Bank Foundation. None of funding bodies had any role in the study design, collection, analysis, or interpretation of data. Nor had the funding bodies any role in the writing of the report, nor in the decision to submit the paper for publication.

Conflict of interest statement. M.I.E. is a shareholder of BCB Medical Oy. D.G. has received lecture or advisory honoraria from AstraZeneca, Boehringer Ingelheim, Fresenius, GE Healthcare, and Novo Nordisk, and support to attend medical meetings from CVRx and Sanofi Aventis. P.S. has received lecture honoraria from Bayer and Santen. T.T. is an advisory board

member of Boehringer. No other potential conflicts of interest relevant to this article were reported. P-H.-G. is an advisory board member of AbbVie, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Sanofi, and has received lecture honoraria from Astellas, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Janssen, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, PeerVoice, Sanofi and SCIARC.

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Table 1. Comparison of individuals with versus without cerebral small-vessel disease

	Small-vessel disease, n = 20	No small-vessel disease, n = 53	p*
Male, n (%)	10 (50.0)	30 (56.6)	0.613[1]
Age, years	42.2 (39.3–46.2)	39.6 (33.4–45.2)	0.113[1]
Diabetes duration, years	20.9 (19.2–32.1)	21.2 (19.9–23.9)	0.748[1]
Diabetes manifestation age, years	19.9 (10.7–24.1)	15.5 (11.0–22.8)	0.638[1]
HbA_{1c}, % [mmol/mol]	8.2 (7.5–8.7) [66 (59–72)]	8.0 (7.4–8.7) [64 (57–72)]	0.647[1]
eGFR, ml/min	106 (95–115)	111 (104–117)	0.122[1]
Body Mass Index, kg/m^2	26.6 (24.6–28.5)	27.1 (24.7–30.4)	0.421[1]
Current smoker, n (%)	0 (0.0)	1 (1.9)	>0.999[1]
Microvascular complications, n (%)	4 (20.0)	11 (20.8)	>0.999[1]
Macrovascular complications, n (%)	0 (0.0)	0 (0.0)	–
Total cholesterol, mmol/l	4.1 (3.7–4.8)	4.4 (4.0–5.0)	0.104[1]
LDL-cholesterol, mmol/l	2.1 (1.4–2.6)	2.3 (2.1–3.0)	0.067[1]
HDL-cholesterol, mmol/l	1.5 (1.3–1.9)	1.5 (1.2–1.8)	0.603[1]
Triglycerides, mmol/l	0.9 (0.7–1.5)	0.9 (0.7–1.3)	0.946[1]
Lipid lowering medication, n (%)	6 (30.0)	12 (22.6)	0.551[1]
Antithrombotic medication, n (%)	2 (10.0)	4 (7.5)	0.528[1]
Antihypertensive medication, n (%)	8 (40.0)	21 (39.6)	0.792[2]
Office SBP, mmHg	133 (124–139)	130 (123–142)	0.270
Office DBP, mmHg	79 (83–75)	81 (74–85)	0.503
Office pulse, /min	69 ± 12	69 ± 12	0.778
24-h SBP, mmHg	127 (124–135)	122 (118–129)	0.078
Diurnal SBP, mmHg	130 (127–140)	127 (122–132)	0.173
Nocturnal SBP, mmHg	117 (111–124)	110 (107–116)	0.010
24-h DBP, mmHg	79 (76–86)	79 (76–83)	0.356
Diurnal DBP, mmHg	82 (79–89)	82 (79–87)	0.648
Nocturnal DBP, mmHg	72 (68-76)	67 (64-72)	0.009
Nocturnal dip, %	11 (6–15)	13 (9–17)	0.050
24-h pulse,1/min	73 (68–82)	72 (66–79)	0.509
Diurnal pulse, 1/min	76 (70–86)	75 (70–84)	0.552
Nocturnal pulse, 1/min	63 (58–68)	62 (56–68)	0.658
24-h MAP, mmHg	95 (90–101)	94 (90–98)	0.416
Diurnal MAP, mmHg	97 (93–104)	97 (93–102)	0.852
Nocturnal MAP, mmHg	86 (83–92)	81 (78–86)	0.006
24-h PP, mmHg	47 (44–52)	44 (41–48)	0.074
Diurnal PP, mmHg	47 (45–53)	44 (41–48)	0.091
Nocturnal PP, mmHg	45 (41–49)	44 (40–47)	0.176
24-h SBP ARV, mmHg	10 ± 3	10 ± 3	0.604
24-h DBP ARV, mmHg	8 (7–9)	7 (6–9)	0.351

Data are presented as mean ± standard deviation and median (inter quartile range). eGFR indicates estimated glomerular filtration rate (CDK-EPI formula); Microvascular complications, albuminuria or retinal photocoagulation; Antithrombotic medication, aspirin or warfarin; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; and ARV, average real variability.

**Adjusted for age, antihypertensive medication, and ambulatory blood pressure monitoring quality*.
[1]Unadjusted p. [2]Adjusted for age and quality only.